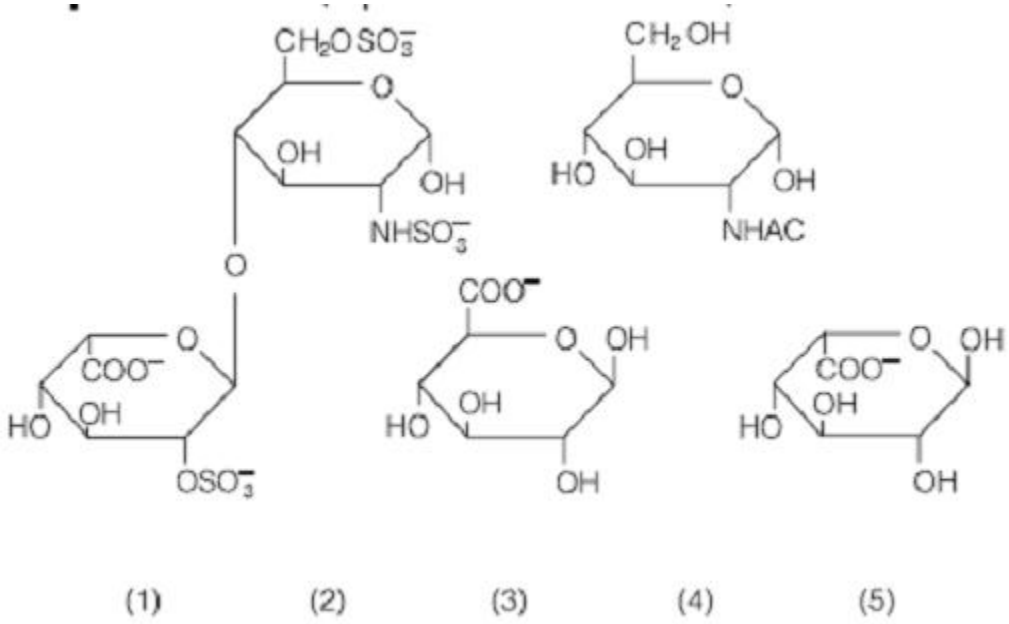
**HEPARIN SODIUM IN DEXTROSE - heparin sodium and dextrose monohydrate injection**
Baxter Healthcare Corporation

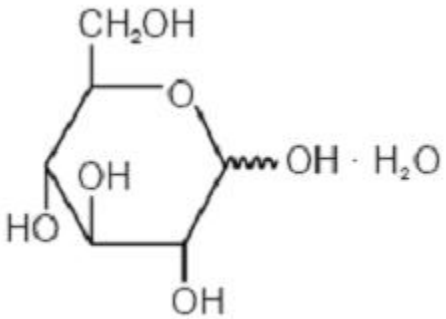
## DESCRIPTION

Heparin Sodium in 5% Dextrose Injection is a buffered, sterile, nonpyrogenic solution of Heparin Sodium, USP, derived from porcine intestinal mucosa, standardized for anticoagulant activity, and dextrose in water for injection. Heparin Sodium, USP, is a heterogenous group of straight-chain anionic mucopolysaccharides, called glycosaminoglycans having anticoagulant properties. Although others may be present, the main sugars occurring in heparin are: (1) α-L-iduronic acid 2-sulfate, (2) 2-deoxy-2-sulfamino-α-D-glucose 6-sulfate, (3) ß-D-glucuronic acid, (4) 2-acetamido-2-deoxy-α-D-glucose, and (5) α-L-iduronic acid. These sugars are present in decreasing amounts, usually in the order (2)> (1) > (4) > (3) > (5), and are joined by glycosidic linkages, forming polymers of varying sizes. Heparin is strongly acidic because of its content of covalently linked sulfate and carboxylic acid groups. In heparin sodium, the acidic protons of the sulfate units are partially replaced by sodium ions. The potency of the heparin is determined by biological assay using USP reference standard based upon units of heparin activity per milligram.

**Structure of Heparin Sodium (representative subunits):**




Dextrose Hydrous, USP, is chemically designated D-gluco pyranose monohydrate, a hexose sugar freely soluble in water. It has the following structural formula:



The solution is intended for intravenous use only. It contains no antimicrobial agents or bacteriostatic agents.
Each 100 mL contains 4,000 or 5,000 or 10,000 USP Heparin Units Heparin Sodium, USP with 5 g Dextrose Hydrous, USP, 103 mg Dibasic Sodium Phosphate Dried, USP ($Na_2HPO_4$) and 51 mg Citric Acid Anhydrous, USP ($C_6H_8O_7$) added as buffers. 20 mg sodium bisulfite is added as a stabilizer. pH 5.5 (5.0 - 6.0). pH may have been adjusted with citric acid and/or sodium hydroxide. Osmolarity 298 mOsmol/L (Actual).
This Viaflex® Plus plastic container is fabricated from a specially formulated polyvinyl chloride (PL 146® Plastic). Viaflex® Plus on the container indicates the presence of a drug additive in a drug vehicle. The Viaflex® Plus plastic container system utilizes the same container as the Viaflex® plastic container system. The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g., di-2-ethylhexyl phthalate (DEHP), up to 5 parts per million.

However, the safety of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

## CLINICAL PHARMACOLOGY

Heparin inhibits reactions that lead to the clotting of blood and the formation of fibrin clots both in vitro and in vivo. Heparin acts at multiple sites in the normal coagulation system. Small amounts of heparin in combination with antithrombin III (heparin cofactor) can inhibit thrombosis by inactivating activated Factor X and inhibiting the conversion of prothrombin to thrombin. Once active thrombosis has developed, larger amounts of heparin can inhibit further coagulation by inactivating thrombin and preventing the conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of the fibrin stabilizing factor.

Bleeding time is usually unaffected by heparin. Clotting time is prolonged by full therapeutic doses of heparin; in most cases, it is not measurably affected by low doses of heparin.

Patients over 60 years of age, following similar doses of heparin, may have higher plasma levels of heparin and longer activated partial thromboplastin times (APTTs) compared with patients under 60 years of age.

Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots.

Peak plasma levels of heparin are achieved 2-4 hours following subcutaneous administration, although there are considerable individual variations. Loglinear plots of heparin plasma concentrations with time for a wide range of dose levels are linear which suggests the absence of zero order processes.

The liver and the reticulo-endothelial system are the sites of biotransformation of heparin. The biphasic elimination curve, a rapidly declining alpha phase ($t1/2 = 10$ minutes), and after the age of 40 a slower beta phase, indicates uptake in organs. The absence of a relationship between anticoagulant half-life and concentration half-life may reflect factors such as protein binding of heparin.

## INDICATIONS AND USAGE

Heparin Sodium is indicated for:

Anticoagulant therapy in prophylaxis and treatment of venous and arterial thrombosis and its extension;

Prophylaxis and treatment of pulmonary embolism;

Atrial fibrillation with embolization;

Diagnosis and treatment of acute and chronic consumption coagulopathies (disseminated intravascular coagulation);

Prevention of clotting in arterial and heart surgery;

Prophylaxis and treatment of peripheral arterial embolism.

## CONTRAINDICATIONS

Heparin sodium should not be used in patients:

With severe thrombocytopenia;

In whom suitable blood coagulation tests - e.g., the whole-blood clotting time, partial thromboplastin time, etc. - cannot be performed at appropriate intervals.

With an uncontrollable active bleeding state (see Warnings), except when this is due to disseminated intravascular coagulation.

Solutions containing dextrose may be contraindicated in patients with known allergy to corn or corn products.

## WARNINGS

### Hypersensitivity:

Patients with documented hypersensitivity to heparin should be given the drug only in clearly life-threatening situations.

### Hemorrhage:

Hemorrhage can occur at virtually any site in patients receiving heparin. An unexplained fall in hematocrit, fall in blood pressure, or any other unexplained symptom should lead to serious consideration of hemorrhagic event.

Heparin sodium should be used with extreme caution in disease states in which there is increased danger of hemorrhage. Some of the conditions in which increased danger of hemorrhage exists are:

Cardiovascular - Subacute bacterial endocarditis. Severe hypertension.

Surgical - During and immediately following (a) spinal tap or spinal anesthesia or (b) major surgery, especially involving the brain, spinal cord, or eye.

Hematologic - Conditions associated with increased bleeding tendencies, such as hemophilia, thrombocytopenia, and some vascular purpuras.

Gastrointestinal - Ulcerative lesions and continuous tube drainage of the stomach or small intestine.

Other - Menstruation, liver disease with impaired hemostasis.

### Coagulation Testing:

When heparin sodium is administered in therapeutic amounts, its dosage should be regulated by frequent blood coagulation tests. If the coagulation test is unduly prolonged or if hemorrhage occurs, heparin sodium should be discontinued promptly (see Overdosage).

**Thrombocytopenia:**
Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0 to 30%. Mild thrombocytopenia (count greater than 100,000/mm3) may remain stable or reverse even if heparin is continued. However, thrombocytopenia of any degree should be monitored closely. If the count falls below 100,000/mm3 or if recurrent thrombosis develops (see White Clot Syndrome, Precautions), the heparin product should be discontinued. If continued heparin therapy is essential, administration of heparin from a different organ source can be reinstituted with caution.
Dextrose solutions with low electrolyte concentrations should not be administered simultaneously with blood through the same administration set because of the possibility of pseudoagglutination or hemolysis. The bag container label for these solutions bears the statement: Do not administer simultaneously with blood.
The intravenous administration of solutions can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states, or pulmonary edema. The risk of dilutional states is inversely proportional to the electrolyte concentrations of the injections. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentrations of the injections.
Heparin Sodium in 5% Dextrose Injection contains sodium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.
Excessive administration of potassium-free solutions may result in significant hypokalemia.

**PRECAUTIONS**

**1. General**

a. White Clot Syndrome
It has been reported that patients on heparin may develop new thrombus formation in association with thrombocytopenia resulting from irreversible aggregation of platelets induced by heparin, the so-called “white clot syndrome”. The process may lead to severe thromboembolic complications like skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke, and possibly death. Therefore, heparin administration should be promptly discontinued if a patient develops new thrombosis in association with thrombocytopenia.

b. Heparin Resistance:
Increased resistance to heparin is frequently encountered in fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer and in postsurgical patients.

c. Increased Risk in Older Patients, Especially Women:
A higher incidence of bleeding has been reported in patients, particularly women, over 60 years of age.

d. Solutions Containing Dextrose:
These solutions should be used with caution in patients with overt or subclinical diabetes mellitis.

e. Use of an electronic flow control device is recommended.
If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

**2. Laboratory Tests**
Periodic platelet counts, hematocrits, and tests for occult blood in stool are recommended during the entire course of heparin therapy, regardless of the route of administration (seeDosage and Administration).

**3. Drug Interactions**
Oral anticoagulants: Heparin sodium may prolong the one-stage prothrombin time. Therefore, when heparin sodium is given with dicumarol or warfarin sodium, a period of at least 5 hours after the last intravenous dose or 24 hours after the last subcutaneous dose should elapse before blood is drawn if a valid prothrombin time is to be obtained.
Platelet inhibitors: Drugs such as acetylsalicylic acid, dextran, phenylbutazone, ibuprofen, indomethacin, dipyridamole, hydroxychloroquine and others that interfere with platelet-aggregation reactions (the main hemostatic defense of heparinized patients) may induce bleeding and should be used with caution in patients receiving heparin sodium.
Other interactions; Digitalis, tetracyclines, nicotine, antihistamines, or intravenous nitroglycerin may partially counteract the anticoagulant action of heparin sodium.

**4. Drug/Laboratory Tests Interactions**
Hyperaminotransferasemia:

Significant elevations of aminotransferase (SGOT [AST] and SGPT [ALT]) levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin. Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, rises that might be caused by drugs (like heparin) should be interpreted with caution.

**5. Carcinogenesis, Mutagenesis, Impairment of Fertility**
No long-term studies in animals have been performed to evaluate carcinogenic potential of heparin. Also, no reproduction studies in animals have been performed concerning mutagenesis or impairment of fertility.

**6. Pregnancy**

Teratogenic Effects

Pregnancy Category C
Animal reproduction studies have not been conducted with heparin sodium. It is not known whether heparin sodium can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Heparin sodium should be given to a pregnant woman only if clearly needed.

Nonteratogenic Effects
Heparin does not cross the placental barrier.

**7. Nursing Mothers**
Heparin is not excreted in human milk.

**8. Pediatric Use**
SeeDosage and Administration.

**9. Geriatric Use**
A higher incidence of bleeding has been reported in patients over 60 years of age, especially women (see Precautions, General). Clinical studies indicate that lower doses of heparin may be indicated in these patients (see Clinical Pharmacology and Dosage and Administration).
Do not administer unless solution is clear and seal is intact.

**ADVERSE REACTIONS**

**1. Hemorrhage**
Hemorrhage is the chief complication that may result from heparin therapy (see Warnings). An overly prolonged clotting time or minor bleeding during therapy can usually be controlled by withdrawing the drug (see Overdosage). It should be appreciated that gastrointestinal or urinary tract bleeding during anticoagulant therapy may indicate the presence of an underlying occult lesion. Bleeding can occur at any site but certain specific hemorrhagic complications may be difficult to detect:
a. Adrenal hemorrhage, with resultant acute adrenal insufficiency, has occurred during anticoagulant therapy. Therefore, such treatment should be discontinued in patients who develop signs and symptoms of acute adrenal hemorrhage and insufficiency. Initiation of corrective therapy should not depend on laboratory confirmation of the diagnosis, since any delay in an acute situation may result in the patient’s death.
b. Ovarian (corpus luteum) hemorrhage developed in a number of women of reproductive age receiving short or long-term anticoagulant therapy. This complication if unrecognized may be fatal.
c. Retroperitoneal hemorrhage.

**2. Local Irritation**
Local irritation, erythema, mild pain, hematoma or ulceration may follow deep subcutaneous (intrafat) injection of heparin sodium. These complications are much more common after intramuscular use, and such use is not recommended.

**3. Hypersensitivity**
General hypersensitivity reactions have been reported, with chills, fever, and urticaria as the most usual manifestations, and asthma, rhinitis, lacrimation, headache, nausea and vomiting, and anaphylactoid reactions, including shock, occurring more rarely. Itching and burning, especially on the plantar site of the feet, may occur.
Thrombocytopenia has been reported to occur in patients receiving heparin with a reported incidence of 0-30%. While often mild and of no obvious clinical significance, such thrombocytopenia can be accompanied by severe thromboembolic complications such as skin necrosis, gangrene of the extremities that may lead to amputation, myocardial infarction, pulmonary embolism, stroke, and possibly death. (See Warnings, Precautions.)
Certain episodes of painful, ischemic, and cyanosed limbs have in the past been attributed to allergic vasospastic reactions. Whether these are in fact identical to the thrombocytopenia associated complications remains to be determined.

**4. Miscellaneous**
Osteoporosis following long-term administration of high-doses of heparin, cutaneous necrosis after systemic administration, suppression of aldosterone synthesis, delayed transient alopecia, priapism, and rebound hyperlipemia on discontinuation of heparin sodium have also been reported.
Significant elevations of aminotransferase (SGOT [AST] and SGPT [ALT]) levels have occurred in a high percentage of patients (and healthy subjects) who have received heparin.
Other reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation and hypervolemia. If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.

## OVERDOSAGE

**Symptoms:**
Bleeding is the chief sign of heparin overdosage. Nosebleeds, blood in urine or tarry stools may be noted as the first sign of bleeding. Easy bruising or petechial formations may precede frank bleeding.

**Treatment:**
Neutralization of heparin effect.
When clinical circumstances (bleeding) require reversal of heparinization, protamine sulfate (1% solution) by slow infusion will neutralize heparin sodium. No more than 50 mg should be administered, very slowly, in any 10 minute period. Each mg of protamine sulfate neutralizes approximately 100 USP heparin units. The amount of protamine required decreases over time as heparin is metabolized. Although the metabolism of heparin is complex, it may, for the purpose of choosing a protamine dose, be assumed to have a half-life of about 1/2 hour after intravenous injection. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions often resembling anaphylaxis have been reported, the drug should be given only when resuscitation techniques and treatment of anaphylactoid shock are readily available.
For additional information the labeling of Protamine Sulfate Injection, USP products should be consulted.

## DOSAGE AND ADMINISTRATION
Heparin Sodium in 5% Dextrose Injection is for intravenous administration only. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Use of a final filter is recommended during administration of all parenteral solutions, where possible.
The dosage of heparin sodium should be adjusted according to the patient’s coagulation test results. When heparin is given by continuous intravenous infusion, the coagulation time should be determined approximately every 4 hours in the early stages of treatment. When the drug is administered intermittently by intravenous injection, coagulation tests should be performed before each injection, during the early stages of treatment, and at appropriate intervals thereafter. Dosage is considered adequate when the activated partial thromboplastin time (APTT) is 1.5 to 2 times normal or when the whole blood clotting time is elevated approximately 2.5 to 3 times the control value. Physicians should refer to medical literature.
Periodic platelet counts, hematocrits, and tests for occult blood in stool are recommended during the entire course of heparin therapy, regardless of the route of administration.

**Converting to Oral Anticoagulant**
When an oral anticoagulant of the coumarin or similar type is to be begun in patients already receiving heparin sodium, baseline and subsequent tests of prothrombin activity must be determined at a time when heparin activity is too low to affect the prothrombin time. This is about 5 hours after the last I.V. bolus and 24 hours after the last subcutaneous dose. If continuous I.V. heparin infusion is used, prothrombin time can usually be measured at any time.
In converting from heparin to oral anticoagulant, the dose of the oral anticoagulant should be the usual initial amount and thereafter prothrombin time should be determined at the usual intervals. To ensure continuous anticoagulation, it is advisable to continue full heparin therapy for several days after the prothrombin time has reached the therapeutic range. Heparin therapy may then be discontinued without tapering.

**Therapeutic Anticoagulant Effect with Full-Dose Heparin**
Although dosage must be adjusted for the individual patient according to the results of suitable laboratory tests, the following dosage may be used as a guideline for continuous intravenous infusion (based on 150 lb [68 kg] patient):

| | |
|---|---|
| Initial Dose: | 5,000 units by I.V. Injection |
| Continuous Dose: | 20,000 - 40,000 units/24 hours |

**Pediatric Use**
Follow recommendations of appropriate pediatric reference texts. In general, the following dosage schedule may be used as a guideline:

| | |
|---|---|
| Initial Dose: | 50 units/kg (I.V., drip) |
| Maintenance Dose: | 100 units/kg (I.V., drip) every four hours, or 20,000 units/M2/24 hours continuously |

**Geriatric Use**
Patients over 60 years of age may require lower doses of heparin.

**Surgery of the Heart and Blood Vessels**
Patients undergoing total body perfusion for open-heart surgery should receive an initial dose of not less than 150 units of heparin sodium per kilogram of body weight. Frequently, a dose of 300 units per kilogram is used for procedures estimated to last less than 60 minutes or 400 units per kilogram for those estimated to last longer than 60 minutes.
All injections in Viaflex® Plus plastic containers are intended for intravenous administration using sterile equipment.
Because dosages of this drug are titrated to response, no additives should be made to Heparin Sodium in 5% Dextrose Injection.

**HOW SUPPLIED**
Heparin Sodium in 5% Dextrose Injection in Viaflex® Plus plastic containers is available as follows:

| Code | Size (mL) | NDC | Product Name |
|---|---|---|---|
| 2B0802 | 250 | 0338-0550-02 | Heparin Sodium 25,000 Units in 5% Dextrose Injection |
| 2B0808 | 500 | 0338-0550-03 | Heparin Sodium 25,000 Units in 5% Dextrose Injection |
| 2B0807 | 500 | 0338-0549-03 | Heparin Sodium 20,000 Units in 5% Dextrose Injection |

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. It is recommended the product be stored at room temperature (25°C); brief exposure up to 40°C does not adversely affect the product.

**Direction for Use of Viaflex® Plus Plastic Container**
Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

**To Open**
Tear overwrap down side at slit and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. Check for minute leaks by squeezing chamber. If external leaks are found, discard solution as sterility or stability may be impaired. Do not add supplementary medication.

**Preparation of Administration**
1. Suspend container from eyelet support.

2. Remove plastic protector from outlet port at bottom of container.

3. Attach solution administration set. Refer to complete directions accompanying set.

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